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AUTISM SPECTRUM DISORDERS (ES BRODKIN, SECTION EDITOR)

Recent Updates in Psychopharmacology for the Core and Associated Symptoms of Autism Spectrum Disorder

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Abstract

Purpose of Review Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by core deficits in social communication and restricted, repetitive patterns of behavior. This article aims to review the recent literature pertaining to psychopharmacology for the core and associated symptoms of ASD including social impairment, repetitive behaviors, irritability, and language impairment.

Recent Findings Recent medication trials targeting social impairment in ASD have focused on neuropeptides (oxytocin and vasopressin) and memantine. None of these three medications has demonstrated consistent benefit for social impairment in ASD; however, additional studies are underway. Two double-blind, placebo-controlled studies on selective serotonin reuptake inhibitors (SSRIs) provide evidence against the use of SSRIs for repetitive behaviors in youth with ASD. Preliminary studies have investigated cannabidiol (CBD) for irritability in ASD but further studies are needed to demonstrate safety and efficacy. Finally, three double-blind, placebo-controlled studies provide preliminary evidence for folinic acid for the treatment of verbal language deficits in children with ASD.

Summary The identification of safe and effective pharmacological treatments to ameliorate the core and associated symptoms of ASD has proven difficult.

Keywords Autism spectrum disorder · Psychopharmacology · Social impairment · Repetitive behaviors · Irritability · Language impairment

Introduction

Autism spectrum disorder (ASD) is a heterogenous neurodevelopmental disorder characterized by core deficits in social communication and restricted, repetitive patterns of behavior [1]. While there are currently no uniformly effective behavioral or psychopharmacological therapies for ASD, management includes early intensive behavioral intervention to improve social functioning and developmental outcomes [2]. Other nonpharmacologic treatments may include intervention for impaired language and communication, social skills training, occupational therapy, and special education. No pharmacologic approaches have been clearly demonstrated to reverse the core symptoms of ASD; however, risperidone and aripiprazole, both second-generation antipsychotic medications, are approved by the United States Food and Drug Administration (FDA) for the treatment of irritability in children and adolescents with ASD. The use of psychopharmacology to treat the associated behavioral symptoms of ASD and co-occurring psychiatric conditions such as

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attention-deficit/hyperactivity disorder, anxiety disorders, and mood disorders is common among individuals with ASD. In fact, a recent large population-based, nationwide, managed health plan claims database study of children and adults with ASD in the USA demonstrated that 59.6% of study participants received a prescription for a psychotropic medication during the 6-year study period [3].

There is an ongoing need for the development of safe and effective pharmacologic treatments for ASD. Psychopharmacology research in ASD over the past 3 years has focused on re-evaluating the efficacy of selective serotonin reuptake inhibitors (SSRIs) for the core symptoms of ASD, assessing whether repurposing medications from other fields of medicine may be an effective approach, and beginning to utilize biologically defined subtypes of ASD to predict treatment response. This article aims to review the recent literature pertaining to psychopharmacology for the core and associated symptoms of ASD including social impairment, repetitive behaviors, irritability, and language impairment. The results of recently published randomized, placebo-controlled trials of psychiatric medications for the core and associated symptoms of ASD are summarized in Table 1.

Social Impairment

Persistent social impairment occurring across multiple contexts is a core symptom of ASD. No pharmacologic treatments have been clearly demonstrated to provide benefit for social impairment in ASD. As such, early intensive behavioral intervention, which has been found to improve learning, communication, and social skills in young children with ASD, remains the standard of care. Several medication trials targeting social impairment in ASD have been published recently, most of which have focused on neuropeptides (oxytocin and vasopressin) and memantine.

Oxytocin is a neuropeptide associated with interpersonal bonding, parenting behaviors, and forming social attachments. Animal models relevant to ASD suggest that dysfunction of the oxytocin system may be involved in the social deficits of ASD and have demonstrated that exogenous oxytocin treatment results in increased social behaviors [4]. Three randomized controlled trials (RCTs) of intranasal oxytocin in adults with ASD have been published in the past 3 years. The first trial was a randomized double-blind, placebo-controlled cross-over trial that enrolled 15 males with ASD and 24 healthy controls (18–26 years) [5]. The participants received either one dose of intranasal oxytocin 20 international units (IU) or placebo spray in a random order on two consecutive days. Unlike the control group, individuals with ASD demonstrated enhanced social learning when given oxytocin compared to placebo. The second study was a 4-week randomized double-blind, placebo-controlled trial with parallel design conducted by Bernaerts et al. where 40 adult males with ASD were randomized to either intranasal oxytocin 24 IU per day or placebo [6]. The primary outcome of interest was social impairment, as measured by self- and informant-rated scores on the Social Responsiveness Scale (SRS) total score. Although improvement on the SRS occurred in both the oxytocin and placebo groups, there was no significant between-group differences ($p = 0.37$). There were significant differences between oxytocin and placebo observed in two of the secondary outcomes measured: reduced feelings of avoidance towards others ($p = 0.03$) and reduced repetitive behaviors ($p = 0.04$) which both persisted one year post-treatment. The third and largest study was a 6-week double-blind, placebo-controlled trial, which randomized 106 adult males (18–48 years) with ASD to either intranasal oxytocin 48 IU per day or placebo [7•]. The primary outcome was the Autism Diagnostic Observation Schedule (ADOS) reciprocity subscale. Similar to results from the trial completed by Bernaerts et al., improvement was observed in both the oxytocin and placebo groups, but oxytocin was not found to be superior to placebo ($p = 0.69$). Oxytocin was, however, associated with a statistically significant improvement compared to placebo in two of the secondary outcome measures: the ADOS repetitive behaviors subscale and duration of gaze fixation on socially relevant eye regions as measured by eye tracking software. Finally, a large, 6-month multi-site phase two trial investigating flexibly dosed intranasal oxytocin (maximum dose 80 IU per day) in 290 children and adolescents (3–17 years) with ASD [8] has completed enrollment and publication of the results is pending. Preliminary indications are that there was no significant difference between oxytocin and placebo on the primary outcome measure, the Aberrant Behavior Checklist (ABC) Social Withdrawal subscale. Taken together, the results from these four trials do not provide convincing evidence to support the use of intranasal oxytocin for the treatment of the core social deficits of ASD.

Vasopressin is a neuropeptide which primarily serves to regulate water reabsorption in the kidneys and increase peripheral vascular resistance. Recent research suggests that vasopressin may also act centrally to regulate and promote social behavior. Two trials assessing vasopressin for the treatment of social deficits in ASD have been published in the past 3 years. Bolognani et al. conducted a randomized placebo-controlled trial of balovaptan, a selective vasopressin V1a receptor antagonist, in 223 adult males (15–40 years) with ASD. Participants were randomized to placebo or one of three balovaptan doses (1.5 mg, 4 mg, or 10 mg per day). Balovaptan treatment was not associated with changes in the SRS-2 [9]. Parker et al. conducted a separate pilot 4-week randomized, double-blind, placebo-controlled trial which included 30 children (6–12 years) with ASD. The maximum dosage of intranasal arginine vasopressin (AVP) was 24 IU per day for children ≤ 9.5 years

Table 1 Select recent randomized, placebo-controlled trials of psychiatric medications in ASD with minimum sample size of 30 subjects

Target symptom	Publication	Medication	Population	Study design	Outcomes
Social impairment	Bernaerts et al. [6]	Oxytocin	40 adult males with ASD	4 weeks Parallel groups	No between-group differences on SRS
	Yamasue et al. [7]	Oxytocin	106 adult males with ASD	6 weeks Parallel groups	No between-group differences on ADOS reciprocity subscale
	Bolognani et al. [9]	Balovaptan	223 adult males with ASD	12 weeks Parallel groups	No between-group differences on SRS-2
	Parker et al. [10]	Vasopressin	30 children (6–12 years) with ASD	4 weeks Parallel groups	Vasopressin group had greater improvement in SRS-2 and CGI-I scores
	Hardan et al. [11]	Memantine	379 children (6–12 years) with ASD who responded to open-label memantine	12 weeks Withdrawal trial	No between-group difference in loss of therapeutic response on SRS
	Karahmadi et al. [12]	Memantine as adjunct to ABA therapy	60 children (< 14 years) with ASD	3 months Parallel groups	Memantine group had greater improvement in GARS total score and social interactions subscale, but no between-group differences on the communication subscale
Repetitive behaviors	Reddihough et al. [16]	Fluoxetine	146 children (7–18 years) with ASD	16 weeks Parallel groups	No between-group differences on CY-BOCS-PDD after controlling for covariates
	Herscu et al. [17]	Fluoxetine	158 children (5–17 years) with ASD	14 weeks Parallel groups	No between-group differences on CY-BOCS-PDD
	Politte et al. [22]	Extended-release guanfacine	62 children (5–14 years) with ASD	8 weeks Parallel groups; analysis of repetitive behaviors as secondary outcome measure	Extended-release guanfacine group had decreased repetitive behaviors on CY-BOCS-ASD
	Sprengers et al. [23]	Bumetanide	92 children (7–15 years) with ASD	13 weeks Parallel groups	No between-group differences on SRS-2
Irritability	Aran et al. [32]	CBD and whole-plant cannabis extract	150 individuals (5–21 years) with ASD	12 weeks Crossover design	CBD was not associated with improvement in disruptive behaviors compared to placebo. Whole-plant cannabis extract resulted in improvement in disruptive behaviors compared to placebo

Table 1 (continued)

Target symptom	Publication	Medication	Population	Study design	Outcomes
Language impairment	Frye et al. [38]	Folinic acid	48 children (3–15 years) with ASD	12 weeks Parallel groups	Folinic acid group had greater improvement in verbal language as measured by the CELF
	Batebi et al. [40]	Folinic acid as adjuvant to risperidone	55 children (4–12 years) with ASD	10 weeks Parallel groups	Folinic acid group had greater improvement on Inappropriate Speech subscale of ABC

ASD, autism spectrum disorder; *SRS*, Social Responsiveness Scale; *ADOS*, Autism Diagnostic Observation Schedule; *CGI-I*, Clinical Global Impressions-Improvement; *ABA*, applied behavior analysis; *GARS*, Gillian Autism Rating Scale; *CY-BOCS-PDD*, Children's Yale-Brown Obsessive Compulsive Scale, modified for pervasive developmental disorder; *CY-BOCS-ASD*, Children's Yale-Brown Obsessive Compulsive Scale, modified for autism spectrum disorder; *CBD*, cannabidiol; *CELF*, Clinical Evaluation of Language Fundamentals; *ABC*, Aberrant Behavior Checklist

and 32 IU per day for children 9.6–12.9 years. In this study, AVP was associated with improved caregiver-reported SRS-2 scores and a clinician-rated Clinical Global Impression-Improvement (CGI-I) score anchored to social-communication abilities compared to placebo ($p = 0.005$) [10]. Arginine vasopressin was well tolerated and there was no difference in the rate of reported adverse effects between AVP and placebo. The findings of this study are tempered by several important limitations including small sample size and reliance on subjective outcome measures.

Memantine, a *N*-methyl-D-aspartate (NMDA) receptor antagonist with FDA approval for the treatment of Alzheimer disease, has been another medication of interest for the treatment of social impairment in ASD. Results from a series of three well-powered, multi-site phase two trials investigating extended-release memantine in children (6–12 years) with ASD were reported by Hardan et al. [11]. The first was a 50-week open-label trial ($n = 906$), the second was a 12-week randomized double-blind placebo-controlled withdrawal trial which enrolled responders from the first trial ($n = 479$), and the third was a ≤ 48 week open-label safety and tolerability extension trial ($n = 747$). Sixty percent of participants demonstrated improvement in SRS scores after 12 weeks of treatment in the open-label phase. In the withdrawal trial, participants were randomized to weight-based full-dose memantine or a dose reduction by ≥ 50%. There was no difference in loss of therapeutic response on the SRS however, between memantine (69%) and placebo (66.7%) in the withdrawal phase. No new safety concerns were observed in the open-label extension trial. In a separate study, Karahmadi et al. investigated memantine as an adjunct to applied behavior analysis (ABA) therapy for children in a small randomized single-blind trial in children (< 14 years) with ASD [12]. Sixty participants were randomized to memantine 2.5 mg twice daily or placebo during a three-month course of ABA therapy. The participants were blinded to treatment assignment. The Gillian Autism Rating Scale (GARS) was completed by the participants' caregiver pre- and post-intervention. The memantine group had a statistically significant improvement compared to placebo in total GARS scores and the GARS social interactions subscale, but there was no between-group difference in the communication subscale. The conclusions of this study are significantly limited by small sample size and the lack of gold standard social and communication measures. Finally, a 12-week RCT of memantine for the treatment of social deficits in youth (8–18 years) with non-verbal learning disorder, high-functioning ASD, and related conditions is currently underway [13]. The results of the double-blind, placebo-controlled withdrawal trial are consistent with the negative results from the original 12-week randomized double-blind, placebo-controlled study of memantine for social impairment in 104 children (6–12 years) with ASD which demonstrated no significant between-group difference on the caregiver-rated SRS [14].

These recently published studies add to our knowledge base of psychopharmacology for social impairment, but do not significantly change current standards of care. The trials assessing oxytocin largely provide evidence against its use in adult males and preliminary indications of the results of a large phase 2 trial in children and adolescents also do not support its efficacy [8]. While recent studies of vasopressin were somewhat promising, there is currently insufficient evidence to support its use clinically. Although the more recent memantine trials demonstrated mixed results [11, 12], it may be worth investigating further and a large RCT of memantine for the treatment of social deficits in youth is currently underway [13].

Repetitive Behaviors

Restricted, repetitive patterns of behavior comprise the second core symptom domain of ASD and include repetitive motor movements, repetitive use of language, circumscribed preoccupations, ritualistic behaviors, difficulty coping with change, and unusual sensory interests. Similar to social impairment, there are no medications currently approved by the FDA for repetitive behavior in ASD. Randomized controlled trials of second-generation antipsychotics, particularly risperidone and aripiprazole, have demonstrated some benefit for repetitive behaviors. A recently published systematic review and meta-analysis including 21 RCTs ($n = 1309$) concluded that antisychotics "probably slightly reduce" repetitive behaviors in children and adolescents with ASD [15]. In light of this weak evidence and the significant side effect burden associated with second-generation antipsychotics including weight gain, metabolic problems, and extrapyramidal symptoms, they are not commonly used for this indication in clinical practice. Alternative safe and effective treatment options remain greatly needed.

The use of SSRIs for the treatment of repetitive behavior in ASD has received significant attention over the years with mixed results. Two recent randomized double-blind, placebo-controlled trials investigating fluoxetine in children and adolescents with ASD add new evidence that SSRIs do not provide benefit for repetitive behaviors compared to placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). Reddihough et al. conducted a 16-week randomized double-blind, placebo-controlled, multi-site trial including 146 children and adolescents (mean age 11.2 years) with ASD [16••]. The primary outcome was the total score on the CY-BOCS, modified for pervasive developmental disorder (CY-BOCS-PDD). Forty-one percent of participants in the fluoxetine group and 36% of participants in the control group discontinued participation. The most common reasons for discontinuation included parent decision to discontinue, adverse events, and clinician decision to discontinue. The most common adverse events were mood disturbance, particularly irritability; gastrointestinal problems; and sleep disorders. Although the between-group mean difference in CY-BOCS-PDD score was statistically significant ($p = 0.03$) at endpoint, fluoxetine was not found to be superior to placebo after controlling for pre-specified covariates including sex, verbal ability, and imbalances in baseline and demographic variables ($p = 0.21$). Similar results were reported by Herscu et al. after completing a 14-week multi-site randomized double-blind, placebo-controlled trial of fluoxetine in 158 children (5–17 years) with ASD [17••]. No significant between-group differences were observed on the CY-BOCS-PDD ($p = 0.06$) and high rates of behavioral activation and adverse events were reported in both groups. Both trials may have encountered limitations inherent to the use of the CY-BOCS-PDD in individuals with ASD [18]. Individuals with ASD experience a range of repetitive behaviors, some of which are pleasurable and others of which are distressing. It is not clear that the CY-BOCS-PDD measures improvement in some of the repetitive behaviors of ASD which may be pleasurable or serve an adaptive function for the individual, yet cause impairment in daily living. Notably, the results from these two trials contrast with results from previous trials which included adults with ASD, suggesting that SSRIs may be more beneficial and better tolerated in post-pubertal individuals [19, 20].

Other pilot studies published within the past 3 years have investigated several other medications including guanfacine, bumetanide, and baclofen for repetitive behaviors in ASD. An analysis of secondary outcome measures of a previously reported 8-week randomized double-blind, placebo-controlled trial of extended-release guanfacine, an alpha-$_2$ agonist, for hyperactivity in 62 youth with ASD (5–14 years) [21], demonstrated significant between-group differences in repetitive behaviors as measured by the CY-BOCS-ASD [22]. Bumetanide, a loop diuretic thought to impact GABA through regulating chloride homeostasis, was assessed in a 91-day randomized double-blind, placebo-controlled trial in 92 youth (7–15 years) with ASD. Bumetanide was not superior to placebo for the primary outcome, the SRS-2, but was superior to placebo for one of the secondary outcomes, the Repetitive Behavior Scale-Revised [23]. Baclofen, a selective $GABA_B$ receptor agonist, was investigated as an adjuvant therapy to risperidone in a 10-week randomized double-blind, placebo-controlled trial including 64 children (3–12 years) with ASD [24]. Improvements in all the ABC subscales were observed in both treatment groups; the adjuvant baclofen group was superior to placebo plus risperidone only on the ABC hyperactivity subscale, indicating that it did not provide additional benefit beyond risperidone for repetitive behaviors. Finally, as discussed in the previous section, two recently published double-blind, placebo-controlled trials of oxytocin for social deficits in ASD noted improvements in repetitive behaviors [6, 7].

In summary, there is no strong evidence for any medication or class of medications for the treatment of repetitive behaviors in ASD. While antipsychotics may be somewhat efficacious, clinical use is limited by their side effect profile. The two recently published double-blind, placebo-controlled studies on SSRIs provide additional evidence against the use of SSRIs for repetitive behaviors in children and adolescents with ASD. There is, however, some new evidence to support the use of extended-release guanfacine for repetitive behaviors.

Irritability

Irritability is common among individuals with ASD and encompasses aggression, self-injurious behavior, property destruction, and severe tantrums. A practice pathway published in *Pediatrics* highlights the need to identify and address the medical, psychiatric, communicative, behavioral, and social factors that may be contributing to disruptive behaviors [25]. If such interventions fail, psychopharmacologic treatments may be necessary. As stated earlier, risperidone and aripiprazole are FDA approved for the treatment of irritability in children and adolescents with ASD. Risperidone's FDA approval was based upon two landmark 8-week randomized double-blind, placebo-controlled trials which each demonstrated significant reductions in irritability in youth with ASD associated with risperidone compared to placebo [26, 27]. Similarly, aripiprazole received its FDA indication for irritability in youth with ASD following the publication of two 8-week randomized double-blind, placebo-controlled trials demonstrating its efficacy [28, 29]. The considerable side effect burden of second-generation antipsychotics and lack of response in some patients have led to an ongoing search for alternative treatments.

Recent investigations have focused on the potential role of cannabidiol (CBD) in the treatment of irritability in ASD. Two prospective, open-label trials and one double-blind, placebo-controlled trial of CBD for irritability in ASD have been published within the past 3 years. The first prospective, open-label trial included 53 individuals (4–22 years) with ASD who received CBD for a median duration of 2 months [30]. Each participant received a preparation of 30% CBD in a ratio of 20:1 cannabidiol:Δ9-tetrahydrocannabinol (THC). Parents reported a change in symptoms of hyperactivity, sleep problems, self-injury, and anxiety on a three-point scale (improvement, no change, or worsening of symptoms). Sixty-eight percent of participants experienced parent-reported improvements in self-injury. The most frequently reported adverse effects included somnolence (22.6%) and appetite suppression (11.3%). The second prospective, open-label study investigated the effectiveness of a medical cannabis product among 188 participants with ASD (mean age 12.9 years) [31]. Most participants used oil with 30% CBD and 1.5% THC sublingually three times daily; however, the route of administration, preparation, dose, and schedule varied among patients. Changes in ASD-associated symptoms including restlessness, rage attacks, agitation, sleep problems, and anxiety were measured at 6 months using a seven-point caregiver scale. Rage attacks and agitation improved among 89% and 84% of participants, respectively. Notably, the dosages of other psychotropic medications were altered in 43% of patients in this study, possibly confounding the effect of the cannabis products. The main limitation of both these studies was the measurement of symptom improvement using unblinded parent reports without the use of a validated scale. The increasingly popular perception that cannabis-derived products have established efficacy for a wide range of conditions suggests that an underlying placebo effect may be partially influencing the results of these two prospective studies. Finally, the variability in the cannabis products, dosage, and route of administration further limits the conclusions that can be drawn from these two prospective, open-label studies.

Aran et al. conducted a 12-week randomized double-blind, placebo-controlled single-site trial studying the efficacy of CBD in 150 individuals (5–21 years) with ASD [32]. Participants were randomized to either whole-plant cannabis extract, pure CBD, or placebo followed by a washout and single crossover period. All participants received a cannabis product in at least one of the two treatment arms. The co-primary outcomes were change in total scores of the Home Situation Questionnaire-ASD (HSQ-ASD) and disruptive behavior measured using the CGI-I. Forty-nine percent of participants who received whole-plant cannabis extract experienced improvement in disruptive behavior (CGI-I = 1 "very much improved" or 2 "much improved"), which was significantly higher than the placebo response rate of 21% ($p = 0.005$). However, the improvement in disruptive behaviors for those treated with pure CBD (38%) was not superior to placebo ($p = 0.08$). Both whole-plant cannabis extract and CBD were generally well tolerated, with somnolence, decreased appetite, tiredness, euphoria, and anxiety being the most commonly reported adverse effects. Since this trial used a particular standardized formulation of CBD, the results may not be generalizable to other CBD oils derived from alternative strains. Limitations of this study include the heterogenous sample, limiting the ability to determine whether a particular subgroup may benefit the most from the use of cannabis-derived products. Additionally, while the crossover design allowed all participants to receive at least one type of cannabis formulation, the researchers were not able to utilize within-participant analyses as they noted a higher change from baseline in the first treatment period compared to the second, suggesting a placebo effect.

At this time, there is insufficient evidence to suggest that CBD be used to target irritability in individuals with ASD. Encouragingly, cannabis-derived products were generally well tolerated, and in fact may be associated with weight loss [32•], a potential advantage over second-generation antipsychotics. However, the relatively short durations of these studies limit the ability to detect potential long-term adverse effects which may be of particular salience in child and adolescent populations. These may include effects on cognition, increased risk of cannabis or other substance use disorders, and other psychiatric disorders (e.g. psychosis, mood disorders, anxiety). There are several challenges in designing high quality clinical trials assessing CBD including the vast

heterogeneity of compounds available and the observation that participants may be able to readily distinguish cannabis products from placebo due to its potentially psychoactive effects. A large, multi-center randomized placebo-controlled trial is warranted to help parcel out potential biases, develop an efficacious standardized formulation, and better assess long-term adverse effects. Until then, the magnitude of potential risks and benefits remain largely unknown. Currently, there are three double-blind randomized controlled trials and one open-label trial underway.

Language Impairment

Current estimates suggest that about a quarter to a third of children with ASD have verbal language deficits [33, 34]. The inability to fully communicate can lead to distress and discomfort that may manifest as agitation and irritability. Currently, the most effective treatment for language impairment associated with ASD includes early intensive behavioral, speech, and educational interventions [35]. At this time, there are no FDA-approved medications for language deficits in ASD. As such, the search for an effective and tolerable pharmacological intervention remains of critical importance. Folinic acid has emerged as a potentially promising candidate [36, 37]. Biochemically, folate metabolism abnormalities have been linked to ASD, including an association with cerebral folate deficiency [37]. Furthermore, the presence of folate receptor-α autoantibodies (FRAAs) may help predict treatment response [36].

Three randomized double-blind, placebo-controlled trials assessing folinic acid for the treatment of language impairment in children with ASD have been published. The first trial included 48 children (3–15 years) with ASD with a wide range of language impairment who were randomized to receive 12 weeks of either high dose folinic acid (two mg/kg per day, maximum 50 mg per day) or placebo [38•]. Baseline and 12-week verbal language skills were assessed using the age-appropriate version of the Clinical Evaluation of Language Fundamentals (CELF). The results of this trial demonstrated a statistically significant improvement in verbal communication in the folinic acid group compared to placebo ($p = 0.02$). Folate receptor-α autoantibody status was predictive of response to treatment. Folinic acid was well tolerated and was not associated with any serious adverse effects.

The second placebo-controlled trial assessed commercially available low dose folinic acid (five mg twice daily) for 12 weeks [39]. The study included 19 children (3–10 years) with ASD and documented language impairments. Similar to the Frye et al. trial [38•], individuals were not excluded based on the severity of their language impairment. The primary outcome measure was the change in ADOS score and secondary outcome measures included the ADOS communication and social interaction subscales. A statistically significant difference in change in global ADOS score between groups was not observed; however, statistically significant greater improvements in the ADOS communication ($p = 0.02$) and social interaction ($p = 0.019$) subscale scores were observed in the folinic acid group compared to placebo.

The third 10-week randomized double-blind, placebo-controlled trial investigated folinic acid as an adjuvant to risperidone for inappropriate speech in 55 children (4–12 years) with ASD [40]. All participants received risperidone plus either high dose folinic acid (2 mg/kg, up to 50 mg per day) or placebo. The primary outcome was change in the Inappropriate Speech subscale of the ABC-Community (ABC-C). Greater improvements in the ABC-C Inappropriate Speech subscale were observed in the folinic acid group compared to the placebo group ($p = 0.045$). Unlike the aforementioned studies, Batebi and colleagues reported a higher rate of adverse effects, including increased appetite and diarrhea, although these observations may be confounded by the concurrent use of risperidone.

Overall, these three studies provide promising preliminary evidence for folinic acid for the treatment of verbal language deficits in children with ASD. However, larger studies of longer duration are needed to provide conclusive evidence, optimize dosing, and further characterize the population (age, type of language deficit) that may be most responsive to treatment. Finally, since these three trials were all single-site studies, multi-site studies are needed to increase generalizability. Encouragingly, there are three ongoing multi-center trials currently registered with clinicaltrials.gov that have yet to publish results. Nevertheless, the overall positive outcomes presented in these early studies and the safety profile of folinic acid are encouraging.

Conclusion

The identification of safe and effective pharmacological treatments to ameliorate the core and associated symptoms of ASD has proven difficult. Psychopharmacology research in this area faces several significant challenges including the heterogeneity of ASD without biologically defined endophenotypes and the inherent difficulty of using a psychotropic medication to reverse neurobiological pathophysiology that likely occurs either prenatally or very early in development. The results from recent clinical trials research over the past few years also underscore high rates of placebo response in this population and the need for outcome measures that are both specific to the target symptoms of interest and capable of detecting change as important factors in study design. Despite these challenges, the field continues to make progress. Recent research has provided more conclusive evidence against the use of some medications such as oxytocin

for social impairment in children, adolescents, and adults and SSRIs for repetitive behaviors in children, as well as some new promising avenues for further study including folinic acid for language impairment.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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